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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number
WO 02/24630 A1

(51) International Patent Classification[7]: C07C 233/22, 233/13, 233/15, 233/11, 233/29, 69/616, 57/74, A61K 31/19, 31/165, A61P 43/00, C07C 235/74, 255/13, 255/29, 69/96, C07D 257/04

(21) International Application Number: PCT/US01/26016

(22) International Filing Date:
10 September 2001 (10.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/234,533 22 September 2000 (22.09.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

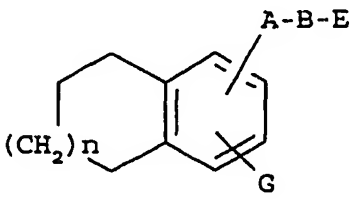
**Declarations under Rule 4.17:**
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 02/24630 A1

(54) Title: PHARMACEUTICAL COMPOUNDS USEFUL AS MODULATORS OF ENDOCANNABINOID-MEDIATED RESPONSE




(I)

(57) Abstract: The present invention provides compounds of formula (I) which are useful for modulating endocannabinoid receptors, pharmaceutical compositions thereof, methods of using the same, processes for preparing the compounds of formula (I) and intermediates thereof.

# PHARMACEUTICAL COMPOUNDS USEFUL AS MODULATORS OF ENDOCANNABINOID-MEDIATED RESPONSE

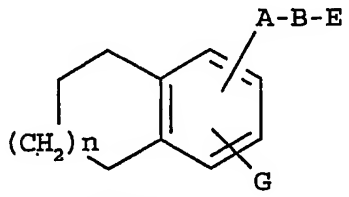
The present invention relates to the fields of pharmacology, medicine, and medicinal chemistry, and provides compounds of formula I, compositions thereof, and methods of using the same for the treatment of various disorders related to endocannabinoid-mediated responses. In addition, the present invention relates to processes for preparing the compounds of formula I and intermediates thereof.

## BACKGROUND OF THE INVENTION

Anandamide (arachidonylethanolamide), an endocannabinoid, is one of the endogenous ligands which activates the receptors involved in the pharmacology associated with the cannabinoid compounds, e.g., $\Delta^9$-tetrahydrocannabinol (THC). The pharmacology of the cannabinoids has been well documented and they exhibit both beneficial as well as detrimental activities. Among the beneficial activities are inhibition of pain, lowering of intra-ocular pressure, inhibition of nausea, increase in appetite, suppression of the immune system. However, also associated with these compounds are detrimental side effects, such as, euphoria, hallucinations, lethargy, etc. The highly lipophilic compounds, such as THC, are super agonists, i.e., they act at the their receptors with greater activity than the endogenous or natural ligand. Additionally, a compound like THC has vastly different pharmacokinetics and metabolic regulation than the endogenous ligand, anandamide. Thus, compounds possessing pharmacological profiles more favorably disposed toward the beneficial aspects are highly desired.

## SUMMARY OF THE INVENTION

The present invention provides compounds of formula I:



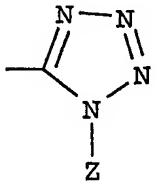

formula I

wherein

A is -O- or a direct bond;

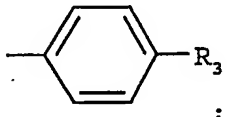
B is $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl or $C_4$-$C_8$ alkenylene;

E is -COOZ, -CONR$^1$Z, or



;

Z is $C_2$-$C_8$R$^2$ or



;

R$^1$ is -H, $C_1$-$C_4$ alkyl, or $C_2$-$C_8$R$^2$;

R$^2$ each time taken, independently, is -H, -halo, -OR$^4$, -CN, or -NR$^5$R$^6$;

R$^3$ is -H, halo, or -OR$^4$;

R$^4$ each time taken, independently, is -H, -COC$_1$-C$_4$ alkyl, or -COAr$^1$ wherein Ar$^1$ is phenyl or optionally substituted phenyl;

R$^5$ is -H, -C$_1$-C$_4$ alkyl, -H, -COC$_1$-C$_4$ alkyl, or -COAr$^2$ wherein Ar$^2$ is phenyl or optionally substituted phenyl;

R$^6$ is -H, -C$_1$-C$_4$ alkyl, -COC$_1$-C$_4$ alkyl, or -COAr$^3$ wherein Ar$^3$ is phenyl or optionally substituted phenyl; or

$R^5$ taken together with $R^6$ and the nitrogen to which they are attached form a 4 to 7 membered ring;
G is -H, $-OC_1$-$C_8$ alkyl, $-OC_2$-$C_8$ alkenyl, $C_1$-$C_8$ alkyl, or $C_2$-$C_8$ alkenyl; and
n is 0-3;

and the pharmaceutically acceptable addition salts thereof.

In another embodiment, the invention provides methods for the modulation of the endocannabinoid receptors with a compound of formula I. Thus, the present invention provides methods for the treatment of the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors comprising administering to a patient in need thereof an effective amount of a compound of formula I. That is, the present invention provides for the use of a compound of formula I or pharmaceutical composition thereof for treating pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors.

A preferred endocannabinoid receptor to be modulated by a compound of formula I would be a receptor which has anandamide as its endogenous ligand. More particularly, anandamide receptors would be CB-1, CB-2, and the anandamide transporter.

Preferred types of modulation of anandamide receptors would be actions by compound of the current invention which antagonize, agonize, or have an allosteric effect.

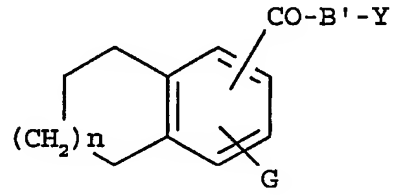
Particularly preferred pathologic sequelae which can be treated according to the present invention include anxiety, pain, glaucoma, depression, feeding disorders, psychosis, and muscle spasms.

In yet another embodiment, the present invention provides for pharmaceutical compositions comprising a compound of the formula I and a pharmaceutically acceptable diluent. Such compositions are useful for treating the

pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors.

Thus, the present invention provides for the use of a compound of formula I for the manufacture of a medicament for treating the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors.

The present invention also provides intermediates for preparing the compounds of formula I. These intermediates include the compounds of formula IV:




formula IV

wherein

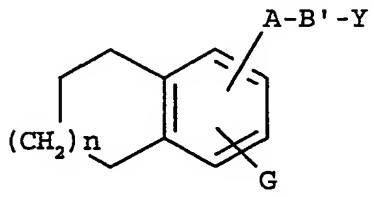
G and n are as described for the compound of formula I;

B' is a $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkylene, or $C_3$-$C_7$ alkenylene; and

Y is halo, or -COOPg.

wherein Pg is either a hydrogen, i.e., a carboxylic acid or a readly removable carboxylic acid protecting group.

The present invention also includes intermediates of the formula:




Wherein

A is oxygen;

G, B', Y, and n are as described for the compound of formula I; and

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the meanings indicated:

The term "$C_1$-$C_8$ alkyl" refers to a straight or branched alkyl chain having from one to eight carbon atoms, and includes methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, t-butyl, pentyl, hexyl, hetpyl, octyl, and the like.

The term "$C_1$-$C_4$ alkyl" refers to a straight or branched alkyl chain having from one to four carbon atoms, and includes methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, and t-butyl.

The term "$C_2$-$C_8$ alkylene" refers to a straight or branched alkylene chain having from two to eight carbon atoms, and includes ethylene, propylene, iso-propylene, butylene, iso-butylene, sec-butylene, 1,1-dimethylmethylene, 1,1-dimethylethylene, 2,2-dimethylethylene, pentylenes, hexylenes, hetpylenes, octylenes, and the like.

The term "$C_4$-$C_8$ alkenylene" refers to a straight or branched carbon chain having from four to eight carbon atoms

with two or more carbon-carbon double bonds, and includes, CH=CH-CH=CH-, $-CH=CHCH_2CH=CH-$, $-CH_2C(CH_3)=CH-CH=CH-$, $-CH=C(CH_3)CH_2-$, and the like.

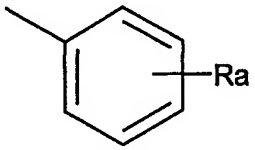
The term "$C_2$-$C_8$ alkenyl" refers to a straight or branched alkene chain having from two to eight carbon atoms, and one or more double bonds and includes vinyl, propylene, iso-propylene, butylene, iso-butylene, sec-butylene, 1,1-dimethylmethylene, 1,1-dimethylethylene, 2,2-dimethylethylene, pentylenes, hexylenes, hetpylenes, octylenes, and the like.

The substituent "$C_2$-$C_8$R" refers to $C_2$-$C_8$ alkyl or branched alkyl, a $C_2$-$C_8$ alkylene or a $C_4$-$C_8$ alkenylene having an R substituent attached at its terminal carbon.

The terms "halo" "halogen" and "halide" refer to a chloro, fluoro, bromo or iodo atom.

The term "-$COC_1$-$C_4$ alkyl" refers to a carbonyl linked to a $C_1$-$C_4$ alkyl.

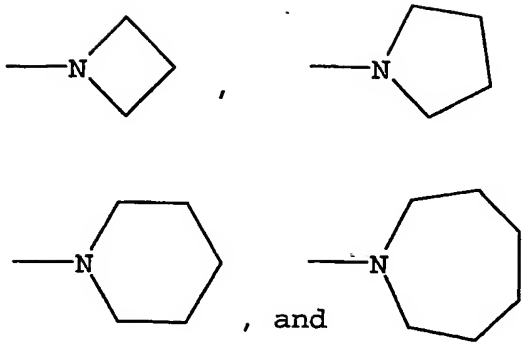
The term "optionally substituted phenyl" refers to a radical of the formula




wherein $R_a$ is from 1 to 3 groups independently selected from the group consisting of hydrogen, $C_1$-$C_4$ alkyl, $C_1$-$C_4$ alkoxy, cyano, nitro, trifluoromethyl, and halogen.

The term "$C_1$-$C_4$ alkoxy" refers to straight or branched alkyl chain having from one to four on atoms attached to an oxygen atom, and includes methoxy, ethoxy, propoxy, iso-propoxy, butoxy, iso-butoxy, sec-butoxy, t-butoxy, and the like.

Examples of substituents in which $R^5$ taken together with $R^6$ and the nitrogen to which they are attached form a 4 to 7 membered ring include the following:



, and

The term "pharmaceutically-acceptable addition salt" refers to an acid addition salt.

The compound of formula I form pharmaceutically acceptable acid addition salts with a wide variety of organic and inorganic acids and include the physiologically acceptable salts which are often used in pharmaceutical chemistry. Such salts are also part of this invention. A pharmaceutically-acceptable addition salt is formed from a pharmaceutically-acceptable acid as is well known in the art. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977) which are known to the skilled artisan. Typical inorganic acids used to form such salts include hydrochloric, hydrobromic, hydriodic, nitric, sulfuric, phosphoric, hypophosphoric, metaphosphoric, pyrophosphoric, and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used. Such pharmaceutically acceptable salts thus include acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, bromide, isobutyrate, phenylbutyrate, α-hydroxybutyrate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, caprate, caprylate,

cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, benzenesulfonate, p-bromobenzenesulfonate, chlorobenzenesulfonate, ethylsulfonate, 2-hydroxyethylsulfonate, methylsulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, nahthalene-1,5-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, and the like.

It is understood that the substituent -A-B-E can be attached to any of the positions of the aromatic ring and that -G can be attached to any of the remaining positions of the aromatic ring. It is also understood that the present invention extends to the stereoisomers and geometric isomers of the compounds of formula I.

As with any group of pharmaceutically active compounds, some groups are preferred in their end use application. Preferred embodiments of the present invention are given below:

Compounds in which n is 1 are preferred.

Compounds in which "A-B-E" occupy the 6-position of the tetrahydronaphthalene moiety are preferred.

Compounds in which E is $-CONR^1Z$ are preferred.

For the compounds in which E is $-CONR^1Z$ the compounds for which $R^1$ is hydrogen are preferred.

For compounds in which Z is $-C_2-C_8R^2$ alkyl, the compounds in which $R^2$ is halo, hydrogen, or hydroxyl are preferred.

When $R^2$ is halo, compounds in which $R_2$ is fluoro are especially preferred.

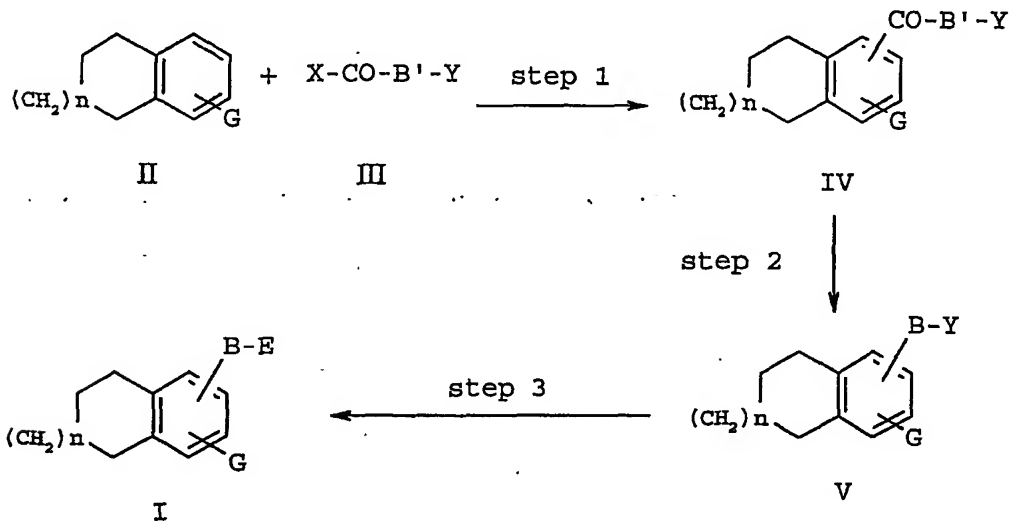
Further for the compounds in which E is $-CONHC_2-C_8R^2$ are preferred, especially when $C_2-C_8R^2$ is ethyl or propyl.

Compounds in which Z is 4-hydroxyphenyl are preferred.

Compounds of formula I may be prepared by methods commonly found in the art of organic chemical synthesis. The compounds of formula I are prepared as described in the Schemes below in which all substituents, unless otherwise indicated, are as previously defined, and all reagents are well known and appreciated in the art.

Compounds of formula I, in which A is a direct bond, may be prepared by the synthetic route outlined in Scheme 1, below:

Scheme 1




In Scheme 1, step 1, an appropriate compound of formula II is acylated with an appropriate compound of formula III to give a compound of formula IV. An appropriate compound of formula II is one in which G and n are as desired in the final product of formula I. An appropriate compound of formula III is one in which B' is a $C_0$-$C_7$ alkyl, $C_2$-$C_8$ alkenyl or $C_2$-$C_7$ alkenylene and give or give rise to B as desired in the final product of formula I; X is halo or taken with Y to form an anhydride, e.g., succinic or glutaric, etc.; Y is halo, -CN, or -COOPg, wherein Pg is carboxyl protecting group. The selection and use of

protecting groups is well known and appreciated in the art. See for example, Protecting Groups in Organic Synthesis, Theodora Greene (Wiley-Interscience). The group Y is further elaborated to give E as desired in the final product of formula I.

For example, an appropriate compound of formula II is contacted with an appropriate compound of formula III under Friedel-Crafts conditions. As is appreciated by the skilled person the position of attachment can be influenced by other substituents present and the such groups as halogen and amino can be used to direct the position of attachment and removed later in the synthetic pathway by methods such as hydrogenation, substitution, diazitization, and the like. Friedel-Crafts conditions include the use of a Lewis acid, a large variety of which are known in the art, e.g., $ZnCl_2$, $AlCl_3$, $AlBr_3$, $FeCl_3$, $PBr_3$, etc: The reaction can be carried out in a variety of inert solvents such as halocarbons, ethers, and the like. Temperatures employed are usually between 0-100°C and the reaction is often complete in 2-24 hours. The product of this step can be isolated and purified by techniques well known in the art, such as filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

In Scheme I, step 2, a compound of formula IV is reduced to give a compound of formula V. Such reductions can be carried out by a variety of methods. These methods will take into account the substituent in Y.

For example, the carbonyl of a compound of formula IV can be reduced by catalytic hydrogenation. Such reactions are carried out in the presence of a catalyst which allows for the reduction of the carbonyl but does not substantially interfere with other functionality in the compound. Suitable catalysts include those of palladium, platinum, nickel, and the like. As is known in the art the catalyst

may be bound to an inert medium, such as carbon. The reaction can be carried out in a variety of inert solvents such as alcohols, acids, ethers, esters and aromatic solvent. The reaction is typically carried at a pressures from atmospheric to about 150 psi. Temperatures employed are usually between ambient temperature and about 100°C. The reaction is often complete in 2-24 hours. The product of this step can be isolated and purified by techniques well known in the art, such as filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

Alternately, for example, the compound of formula IV can be reduced to a hydroxyl followed by further reduction or elimination. Reduction to a hydroxyl can be effected by metal hydrides, such as lithium aluminumhydride, sodium borohydride, and the like. Such reductions are carried out in solvents, such as, for lithium aluminumhydride, ethers and, for sodium borohydride, alcohols. Temperatures employed are usually between ambient temperature and the refluxing temperature of the solvent. The reaction is often complete in 1-24 hours. The hydroxyl product can be further reduced, either directly or after conversion to a halide. Alternately, the hydroxyl can be eliminated, either directly or after conversion to an group which is activated to elimination, such as halides or sulfonates. The product of this step can be isolated and purified by techniques well known in the art, such as filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

As an alternative, not shown in Scheme 1, compounds of formula V can be prepared directly by Friedel-Crafts alkylation, under standard Friedel-Crafts conditions, using appropriate alkyl halides. Such appropriate alkyl halides include compounds of the formula X-B'-Y as desired in the

final product of formula I; X is halo and Y is as defined above. Such alkylations are carried out, as is appreciated in the art, in a manner similar to the acylations described in Scheme 1, step 1, above. Such alkylations give a compound of formula V directly, that is, without reduction of the intermediate acyl compound of formula IV.

In Scheme 1, step 3, a compound of formula V is converted to a compound of formula I. In step 3, a protected compound of formula V is modified or deprotected and modified, as needed, to give a compound of formula I.

A compound of formula I in which E is -COOZ and -CONR$^1$Z are readily prepared from a compound of formula V in which Y is -COOPg by transesterification or by deprotection followed by ester or amide formation. Such ester and amide formation reactions can be carried out utilizing a variety of techniques.

For example, suitable ester and amide formation reactions use of active ester leaving groups. The formation and use of active ester leaving groups used is well known and appreciated in the art. Active ester leaving groups include but are not limited to anhydrides, mixed anhydrides, acid chlorides, acid bromides, 1-hydroxybenzotriazole esters, 1-hydroxysuccinimide esters, or the activated intermediates formed in the presence of coupling reagents, such as dicyclohexylcarbodiimide, 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide, and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinolone.

One suitable ester formation involves the use of an acid chloride followed by reaction with an appropriate alcohol, HOZ. An appropriate alcohol, HOZ, is one in which Z is as desired in the final product of formula I. Acid chlorides are formed from acids by the action of thionyl chloride or oxalyl chloride, with or without a small amount of dimethylformamide, in an inert solvent such as, toluene,

benzene, methylene chloride, or chloroform; at temperatures of from about 0-80°C. The reaction is typically carried out for a period of time ranging from 1 hour to 24 hours. The acid chloride can be isolated and purified or can often be used directly, that is, with or without isolation. Ester formation is carried out by contacting the acid chloride and an and appropriate alcohol, HOZ. The reaction is carried out in an inert solvent, such as toluene, methylene chloride, or chloroform and in the presence of a base, such as pyridine, triethylamine, N-methylmorpholine; and at temperatures of from about 0-80°C. The reaction is typically carried out for a period of time ranging from 1 hour to 12 hours. The product can be isolated and purified by techniques well known in the art, such as quenching, extraction, evaporation, chromatography, and recrystallization.

Compounds in which E is $-CONR^1Z$ are prepared by amidation reactions using an appropriate amine, $NHR^1Z$. An appropriate amine, $NHR^1Z$, is one in which $R^1$ and Z is as desired in the final product of formula I. The amide formation reaction is carried out using an active ester leaving groups, in an solvent suitable for the selected active ester, such as alcohols, water, toluene, methylene chloride, or chloroform. The reaction is typically carried out in the presence of a base, such as pyridine, triethylamine, N-methylmorpholine, sodium carbonate, sodium bicarbonate, and sodium hydroxide and at temperatures of from about 0-100°C. The reaction is typically carried out for a period of time ranging from 1 hour to 12 hours. The product can be isolated and purified by techniques well known in the art, such as quenching, extraction, evaporation, chromatography, and recrystallization.

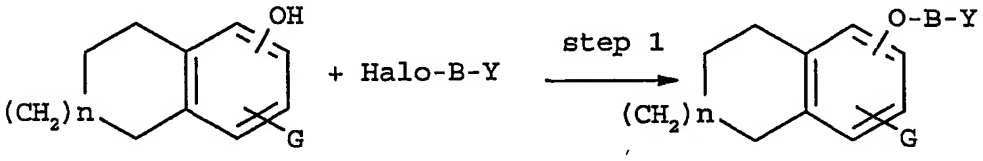
Compounds of formula I, where E is a tetrazole may be synthesized by procedures commonly known in the art of

organic chemistry. For example, compounds of formula I where E is a tetrazole may be synthesized from the corresponding nitrile by reaction with sodium azide and ammonium chloride at elevated temperature in an inert solvent such as DMF [See: Marshall *et al.*, J. Med. Chem., 30, (4), pp. 682-689 (1987)]. Similarly, the tetrazoles may be prepared from the same nitriles by reaction with tributyltin azide. The tetrazole intermediates may be converted to the compounds of formula I by alkylation of the tetrazole nitrogen with an appropriate halo-reagent, e.g., the ethylhydroxy analog may be prepared from bromoethanol, etc. N-alkylation of this type are well known in the art and are usually carried out with a bromo, iodo, or chloro reagent in the presence of a base, such as potassium carbonate in an inert solvent such as methylethylketone at refluxing temperature.

In Scheme 1, optional step 4, not shown, an acid addition salt is formed using a pharmaceutically-acceptable acid. The formation of acid addition salts is well known and appreciated in the art.

Compounds of formula I, where A is -O-, may be prepared by the methods outlined in Scheme 2, below:

Scheme 2




VI VII VIII

In Scheme 2, step 1, an appropriate compound of formula VI is acylated with an appropriate compound of formula VII to give a compound of formula VIII. An appropriate compound of formula VI is one in which G and n are as desired in the final compound of formula I. An appropriate compound of formula VII is one in which B and Y are as defined above.

For example, a compound of formula VI is alkylated with a compound of formula VII to give a compound of formula VIII. Such alkylations of phenolic hydroxyls are well known in the art and may be accomplished by using a organic or inorganic base such as sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, triethylamine, N-ethyldiisopropylamine, and the like. Such reactions may be carried out in an inert solvent such as alcohols, ethers, aromatic solvents, and dimethylformamide, dichloromethane and are carried out at temperatures from 0° to 100°C for a time period of 2-48 hours. The product of this step can be isolated and purified by techniques well known in the art, such as filtration, extraction, evaporation, trituration, chromatography, and recrystallization.

The compound of formula VIII can be modified as described in Scheme 1, step 3, to provide the group E as desired in the final product of formula I. Once formed the compound of formula I prepared by Scheme 2 it can form an acid addition salt using a pharmaceutically-acceptable acid as described in Scheme 1, optional step 4, he formation of such acid addition salts is well known and appreciated in the art.

The present invention is further illustrated by the following examples and preparations. These examples and preparations are illustrative only and are not intended to limit the invention in any way.

The terms used in the examples and preparations have their normal meanings unless otherwise designated. For example, "°C" refers to degrees Celsius; "M" refers to molar or molarity; "mmol" refers to millimole or millimoles; "g" refers to gram or grams; "mL" refers milliliter or milliliters; "L" refers to liter or liters, and "brine" refers to a saturated aqueous sodium chloride solution, etc.

Preparation 1

4-[6-(1,2,3,4-tetrahydronaphthyl)]-4-ketobutyric acid

The following materials were placed in a 1L flask: 26.4g (0.2 mole) of 1,2,3,4-tetrahydronaphthalene, 20g (0.2 mole) of succinic anhydride, and 500 mL of dichloromethane. This solution was cooled to 0° C in an ice bath. Slowly over a period of approximately fifteen minutes 40g (0.3 mole) of $AlCl_3$ was added. The reaction was allowed to proceed for sixteen hours. The reaction was allowed to slowly rise to ambient temperature and the reaction vessel was fitted with a drying tube to maintain anhydrous conditions. The reaction was quenched by pouring over an ice-water slurry. The methylene chloride layer was removed and the aqueous layer was extracted (2x) with additional methylene chloride. The combine methylene chloride extracts were washed with dilute HCl, and then with brine. The resulting solution was dried by filtration through anhydrous $Na_2SO_4$ and evaporated to dryness, *in vacuo* . This procedure yielded 29.26g of the title compound as a tan amorphous powder with the following characteristics:

PMR: consistent with the proposed structure, a small amount of the 5-naphthyl derivative was present.

MS: m/z=231 (M-1) ES-.

Preparation 2

5-[6-(1,2,3,4-tetrahydronaphthyl)]-5-ketopentanoic acid

In a manner similar to the above preparation, the title compound was prepared from the reaction of 13.2g (0.1 mole) of 1,2,3,4-tetrahydronaphthalene with 12.4g (0.11 mole) of glutaric anhydride and 26g (0.2 mole) of aluminum chloride. This procedure yielded 11.7g of the title compound as a tan solid.

PMR: Consistent with the proposed structure.

MS: m/z=245 (M-1) ES-.

Preparation 3

6-[6-(1,2,3,4-tetrahydronaphthyl)]-6-ketohexanoic acid

In a manner similar to that used in Preparation 1, 6.6g (0.05 mole) of 1,2,3,4-tetrahydronaphthalene, 9g (0.05 mole) of methyloxyadipoyl chloride, and 13.8g (0.1) mole of aluminum chloride were utilized to produce 9.79g of the methyl ester derivative of the title compound. The title compound was prepared by the hydrolysis of the ester with sodium hydroxide.

PMR: Consistent with the proposed structure.

MS: m/e=261 (M+1) FD.

Preparation 4

5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoic acid

5-[6-(1,2,3,4-tetrahydronaphthyl)]-5-ketopantanoic acid, 11.7g (0.048 mole), was dissolved in 130 mL of glacial acetic acid and 5 mL of conc. sulfuric acid. To this solution was added 3g of 5%Pd/C and the reaction was run in a hydrogen atmosphere @ 40psi, at a temperature of 40°C for eight hours. The catalyst was filtered off and the solvent removed by evaporation. The residue was dissolved in EtOAc and extracted twice with 1N NaOH. The combined aqueous extracts were made acidic with the addition of HCl and the resulting suspension was extracted twice with EtOAc. The EtOAc extracted were dried by filtration through anhydrous $Na_2SO_4$ and evaporation of the volatilize yielded 6.89g of the title compound.

PMR: Consistent with the proposed structure.

IR: 1709 $cm^{-1}$ ($CHCL_3$)

MS: m/e=231 (M-1) -Q1.

Preparation 5

4-[6-(1,2,3,4-tetrahydronaphthyl)]butyric acid

In a similar manner as Preparation 4, 25.9g (0.11 mole) of the corresponding keto derivative was converted to the

title compound by reduction with hydrogen at 60 psi, at 40°C, for eight hours with 6.5g of 5% Pd/C in a solvent of 500 mL of glacial acetic acid and 12 mL of conc. sulfuric acid. This yielded 13.1g of the title compound as a tan solid.

PMR: Consistent with the proposed structure.

IR: 1708 $cm^{-1}$ ($CHCl_3$)

MS: m/e=217 (M-1) -Q1

Preparation 6

6-[6-(1,2,3,4-tetrahydronaphthyl)]hexanoic acid

In a manner similar to Preparation 4, 6-[6-(1,2,3,4-tetrahydronaphthyl)]-6-ketohexanoic acid, 1.1g (4.2 mmole), was reduced with hydrogen at 60psi, at 40°C, for eight hours, with 5% Pd/C, in a solvent of 50 mL of glacial acetic acid and 5 mL of conc. sulfuric acid. This yielded 730mg of the title compound as a tan amorphous powder.

PMR: Consistent with the proposed structure.

MS: m/e=245 (M-1) -Q1

Preparation 7

5-[6-oxy(1,2,3,4-tetrahydronaphthalyl)]pentanoic acid

The methyl ester derivative was prepared by reaction of 1,2,3,4-tetrahydro-6-naphthol 3g (20 mmole) with methyl-5-bromopentanoate 7.7g (40 mmole) and 8.3g (60 mmole) of anhydrous $K_2CO_3$ in 100 mL of methylethylketone. The mixture was refluxed for eighteen hours. The reaction was quenched by filtration followed by evaporation of the solvent, *in vacuo*. The residue was redissolved in EtOAc and extracted twice with brine, filtered through anhydrous $Na_2SO_4$ followed by evaporation of the solvent. This yielded the methyl ester intermediate of the title compound.

PMR: Consistent with the proposed structure.

MS: m/e=263 (M+1) +Q1

The methyl ester was hydrolyzed to the title compound by dissolution in 75 mL of MeOH and 75 mL of 1N NaOH and

heating the mixture to reflux temperature sixty hours. The reaction volume was reduced by 50% by evaporation of the methanol, followed by acidification with 1 N HCl and extraction (2X) with EtOAc. The combined EtOAc extract was dried with $Na_2SO_4$ and evaporated to dryness. This yielded 3.05g of the title compound as a tan amorphous powder.

PMR: Consistent with the proposed structure.

MS: m/e=249 (M+1) +Q1; m/e=248 (M) FD.

Preparation 8

8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoic acid

In a manner similar to Preparation 7, 2.08g (14 mmole) of 1,2,3,4-tetrahydro-6-naphthol, 3.9g (16.5 mmole) of 8-bromo-methyloctanoate, and 4.1g (30 mmole) of $K_2CO_3$ were converted to 3.12g of the methyl ester derivative of the title compound.

PMR: Consistent with the proposed structure.

MS: M/e=305 (M+1) +Q1

The methyl ester was hydrolyzed in a manner similar to Preparation 7, which yielded 2.45g of the title compound as a tan amorphous powder.

PMR: Consistent with the proposed structure.

MS: m/e=289 (M-1) -Q1; M/e=291 (M+1) +Q1.

Preparation 9

6-[6-oxy(1,2,3,4-tetrahydronaphthyl)]hexanoic acid

In a manner similar to Preparation 7, 3.0g (20.3 mmole) of 1,2,3,4-tetrahydro-6-naphthol, 4.6g (22.0 mmole) of 6-bromo-methylhexanoate, and 12.0g (86 mmole) of $K_2CO_3$ were converted to 6.10g of the methyl ester derivative of the title compound.

PMR: Consistent with the proposed structure.

MS: M/e=277 (M+1) +Q1

The methyl ester was hydrolyzed in a manner similar to Preparation 7, which yielded 3.88g of the title compound as a white powder.

PMR: Consistent with the proposed structure.

MS: m/e=261 (M-1) -Q1.

Preparation 10

6-(4-Cyanobutyloxy)-1,2,3,4-tetrahydronaphthalene

The title compound was prepared by the reaction of 7.4g (50 mmole) of 1,2,3,4-tetrahydro-6-naphthol, 8.1g (50 mmole) of 1-bromo-4-cyanobutane, and 13.8g (100 mmole) of $K_2CO_3$, in a manner similar to Preparation 7. This procedure yielded 6.96 g of the title compound as a light brown oil.

PMR: Consistent with the proposed structure.

MS: m/e=230 (M-1) +Q1.

Preparation A

6-(3-Cyanopropyloxy)-1,2,3,4-tetrahydonaphthalene

The title compound was prepared in a manner analogous to that used in Preparation 10, *supra*. This yielded the title compound as a light brown oil.

PMR: Consistent with the proposed structure.

MS: m/e=216 (M+1) ES+.

Preparation 11

6-[4-(5-tetrazoyl)butyloxy)-1,2,3,4-tetrahydronaphthalene

A suspension was prepared consisting of 2310mg (10 mmole) of 6-(4-cyanobutyloxy)naphthalene, 1950 mg (30 mmole) of $NaN_3$, and 1620 mg (30 mmole) of $NH_4Cl$ in 125 mL of DMF. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere for sixteen hours. The solvent was removed by evaporation, *in vacuo*. The residue was dissolved in EtOAc and extracted with 2N NaOH. The aqueous layer was extracted with EtOAc and acidified with 5N HCl forming a white precipitate. The acidified reaction mixture was extracted twice with EtOAc. The organic solution was dried by filtration through anhydrous $Na_2SO_4$ and evaporated to dryness. This procedure yielded the title compound as tan solid.

PMR: Consistent with the proposed structure.

Preparation B

6-[3-(5-tetrazoyl)propyloxy]-1,2,3,4-tetrahydronaphthalene

The title compound was prepared in a manner analogous to that used in Preparation 11, *supra*. The title compond was isolated as a white solid.

PMR: Consistent with the proposed structure.

MS: m/e=258 (M) FD.

Preparation 12

[4-[6-(1,2,3,4-tetrahydronaphthyl)]-1-oxobutane][iso-butyl]carbonate

A solution was prepared of 600mg (2.75 mmole) of 4-[6-(1,2,3,4-tetrahydronaphthyl)]butric acid and 350 mg (3.5 mmole) of triethylamine in 50 mL of anhydrous THF and cooled to 0°C. An aliquot of 410 mg (3.0 mmole) of iso-butylchloroformate was added and the reaction was stirred under a dry atmosphere, and allowed to proceed for several hours. An additional 25 mL of THF was added. The resulting solution (without further purification) was used to synthesize the following examples.

In an analogous manner to that of Preparation 12, the following Preparations were performed:

Preparation 13

[5-[6-(1,2,3,4-tetrahydronaphthyl)]-1-oxopentane][iso-butyl]carbonate

Preparation 14

[6-[6-(1,2,3,4-tetrahydronaphthyl)]-1-oxohexane][iso-butyl]carbonate

Preparation 15

[5-[6-oxy(1,2,3,4-tetrahydronaphthyl)]-1-oxopentane][iso-butyl carbonate

Preparation 16

[6-[6-oxy(1,2,3,4-tetrahydronaphthyl)]-1-oxohexane][iso-butyl carbonate

Preparation 17

[8-[6-oxy(1,2,3,4-tetrahydronaphthyl)]-1-oxooctane][iso-butyl carbonate

Example 1

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-hydroxyethyl]amide

A suspension of 0.9 mmole of the activated carboxylic acid, i.e., 25 mL of the product of Preparation 11, was added to a solution of 600mg (1 mmole) ethanolamine in THF. The reaction was allowed to proceed with stirring at ambient temperature, under a dry atmosphere for sixteen hours. The reaction mixture was evaporated to dryness, *in vacuo*, and redissolved in a mixture of EtOAc with a small amount of MeOH. The resulting solution was extracted twice with brine. The organic layer was dried by filtration through anhydrous $Na_2SO_4$ and evaporated to an oil, which solidified upon standing. This procedure yielded 90mg of the title compound as a tan solid.

PMR: Consistent with the proposed structure.

IR: 1658 $cm^{-1}$ ($CHCL_3$)

MS: m/e=262 (M+1) +Q1

The following Examples were made in a analogous manner as that provided in Example 1.

Example 2

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-3-hydroxypropyl]amide

PMR: Consistent with the proposed structure.

IR: 1653 $cm^{-1}$ ($CHCl_3$)

MS: m/e=276 (M+1) Q+

Example 3

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-3-hydroxyprop-2-yl]amide

PMR: Consistent with the proposed structure.

IR: 1656 $cm^{-1}$ ($CHCl_3$)

MS: m/e=276 (M+1) Q+

Example 4

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=264 (M+1) Q+

Example 5

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-4-fluorophenyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=312 (M+1) +Q

Example 6

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-cyanoethyl]amide

PMR: Consistent with the proposed structure.

MS: M/e=271 (M+1) +Q

Example 7

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][2-hydroxyethyl]ester

PMR: Consistent with the proposed structure.

MS: M/e=263 (M+1) +Q

Example 8

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl]amide

PMR: Consistent with the proposed structure.

IR: 1680 $cm^{-1}$ ($CHCl_3$)

MS: m/e=232 (M+1) +Q.

Example 9

[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure.

MS: M/e=278 (M+1) ES+

Example 10

[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=324 (M+1) ES+; m/e=322 (M-1) ES-

Example 11

[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-2-hydroxyethyl]amide

PMR: Consistent with the proposed structure

MS: m/e=276 (M+1) ES+

Example 12

[6-[6-(1,2,3,4-tetrahydronaphthyl)]hexanoyl][N-3-hydroxpropyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=304 (M+1) +Q

Example 13

[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure

MS: m/e=382 (M+1) +Q

Example 14

[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-3-hydroxypropyl]amide

PMR: Consistent with the proposed structure

MS: m/e=348 (M+1) +Q

Example 15

[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure

MS: m/e=336 (M+1) +Q

Example 16

[6-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure

MS: m/e=308 (M+1) +Q

Example 17

[6-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]hexanoyl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure

MS: m/e=352 (M-1) -Q

Example 18

[5-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-3-hydroxypropyl]amide

PMR: Consistent with the proposed structure

MS: m/e=306 (M+1) +Q

Example 19

[5-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure

MS: m/e=340 (M+1) +Q

Example 20

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-4-hydroxyphenyl]amide

A solution of 440mg (2.0 mmole) of 5-[6-(1,2,3,4-tetrahydronaphthyl)]butric acid, 1600mg (8.0 mmole) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 550mg (5.0 mmole) of p-hydroxyaniline, in 50 mL of methylene chloride was prepared. The reaction mixture was stirred and kept under a dry atmosphere. The reaction was allowed to proceed for 144 hours at ambient temperature. The reaction mixture was evaporated to dryness and redissolved in EtOAc.

The organic layer was extracted twice with brine, dried by filtration through anhydrous $Na_2SO_4$, and evaporated to dryness. The crude product was chromatographed on silica gel eluted with EtOAc-hexane (1:1) (v/v). The product was crystallized out of EtOAc. This procedure yielded 70mg of the title compound.

PMR: Consistent with the proposed structure.

MS: m/e=310 (M+1) +Q

Example 21

[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-3-hydroxypropyl]amide

In a manner similar to that of Example 18, 464mg (2mmole) of 5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoic acid, 575mg (3.0 mmole) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 300mg (4.0 mmole) of 3-hydroxypropylamine, were converted to 70mg of the title compound.

PMR: Consistent with the proposed structure.

MS: m/e=290 (M+1) +Q

Example 22

[5-[4-(6-oxy-1,2,3,4-tetrahyronaphthyl)butyl]][1-N-2-hydroxyethyl]tetrazole

A suspension was prepared consisting of 100mg (0.37 mmole) of 5-[4-(6-oxy-1,2,3,4-tetrahyronaphthalene) butyltetrazole, 100mg (0.83 mmole) of 2-bromoethanol, and 200mg (1.45 mmole) of $K_2CO_3$ in 25 mL of methylethylketone. The reaction mixture was stirred under a dry atmosphere at reflux temperature for sixteen hours. The reaction mixture was filtered and evaporated to dryness. The residue was dissolved in EtOAc and with dilute NaOH and then with brine. The organic layer was dried by filtration anhydrous $Na_2SO_4$ and evaporation to dryness. This afforded 100mg of the title compound as a tan amorphous powder.

PMR: Consistent with the proposed structure.

MS: m/e=317 (M+1) ES+.

Preparation 18

4-(5-indanyl)-4-oxobutyric acid

In a manner similar to that described in Preparation 1, the title compound was prepared.

PMR: Consistent with the proposed structure.

MS: m/e=217 (M-1) ES-.

Preparation 19

4-(5-indanyl)butyric acid

In a manner similar to that described in Preparation 4, the title compound was prepared.

PMR: Consistent with the proposed structure.

MS: m/e=203 (M-1) ES-

Preparation 20

4-(7-benzosuberanyl)-4-oxobutyric acid

In a manner similar to that described in Preparation 1, the title compound was prepared.

PMR: Consistent with the proposed structure.

MS: m/e=247 (M+1) ES+

M/e=245 (M-1) ES-

Preparation 21

4-(7-benzosuberanyl)butyric acid

In a manner similar to that described in Preparation 4, the title compound was prepared.

PMR: Consistent with the proposed structure.

MS: m/e=232 (M+) FD

Preparation 22

[4-(5-indanyl)-1-oxobutane][iso-butyl]carbonate

Preparation 23

[4-(7-benzosuberanyl)-1-oxobutane][iso-butyl]carbonate

The following Examples were made in a analogous manner as that provided in Example 1.

Example 23

[4-(5-indanyl)butyryl][N-2-hyrdoxyethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=248 (M+1) ES+

EA: Calc.; C 72.84, H 8.56, N 5.66: Found; C 72.65, H 8.54, N 5.67.

Example 24

[4-(5-indanyl)butyryl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=250 (M+1) ES+

EA: Calc.; C 72.26, H 8.09, N 5.62: Found; C 71.99, H 8.13, N 5.64.

Example 25

[4-(5-indanyl)butyryl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=296 (M+1) ES+; m/e=294 (M-1) ES-

EA: Calc.; C 77.26, H 7.17, N 4.74: Found; C 76.63, H 7.11, N 4.77.

Example 26

[4-(7-benzosuberanyl)butyryl][N-2-hyrdoxyethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=276 (M+1) ES+

EA: Calc.; C 74.14, H 9.15, N 5.09: Found; C 74.34, H 9.12, N 5.13.

Example 27

[4-(7-benzobuberanyl)butyryl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=278 (M+1) ES+

EA: Calc.; C 73.61, H 8.72, N 5.05: Found; C 73.75, H 8.76, N 5.12.

Example 28

[4-(7-benzosuberanyl)butyryl][N-4-hydroxyphenyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=324 (M+1) ES+

M/e=322 (M-1) ES-

EA: Calc.; C 77.99, H 7.79, N 4.33: Found; C 77.85, H 7.65, N 4.37.

Preparation 24

[6-(1,2,3,4-tetrahydronaphthyl)][5-pentyl]ketone

A solution was prepared with 6.6g (0.05 mole) of 1,2,3,4-tetrahydronaphthalene and 8.1g (0.06 mole) of n-hexanoyl chloride in 250 mL of methylene chloride. The solution was cooled in an ice bath and 8g (0.06 mole) of $AlCl_3$ was slowly added. The reaction mixture was stirred for sixteen hours, under a nitrogen atmosphere, slowly warming to ambient temperature. The reaction mixture was poured into ice and separated. The organic layer was washed sequentially with 1N HCl, 1N NaOH, and water. The solution was dried by filtration through anhydrous sodium sulfate and evaporated to dryness. This yielded 8.5g of the title compound as a oily solid.

PMR: Consistent with the proposed structure.

MS: m/e=230 (M+) EI+

Preparation 25

6-hexyl-1,2,3,4-tetrahydronaphthalene

The ketone from Preparation 24 was reduced to the corresponding alkyl in a manner similar to that described in Preparation 4, *supra*. This yielded 5.1g of the title compound as a tan oily solid.

PMR: Consistent with the proposed structure.

MS: m/e=216 (M+) EI+

Preparation 26

4-[7-(6-hexyl-1,2,3,4-tetrahydronaphthyl)]-4-ketobutyric acid

In a manner analogous to that described in Preparation 1, 4.12g of the title was prepared.

PMR: Consistent with the proposed structure.

MS: m/e=316 (M) FD

Preparation 27

4-[7-(6-hexyl-1,2,3,4-tetrahydronaphthyl)]butyric acid

In a manner analogous to that described in Preparation 4, the ketone from Preparation 26 was reduced to the alkyl analog. This yielded 2.45g of the title.

PMR: Consistent with the proposed structure.

MS: m/e=301 (M-1) ES-

Preparation 28

[4-[7-(6-hexyl-1,2,3,4-tetrahydronaphthyl)]-1-oxobutane][iso-butyl]carbonate

This compound was prepared in a manner as described in Preparation 12, *supra*.

The following Examples were made in a analogous manner as that provided in Example 1.

Example 29

[4-(6-hexyl-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=346 (M+1) ES+

Example 30

[4-(6-hexyl-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide

PMR: Consistent with the proposed structure.

MS: m/e=348 (M+1) ES+

Preparation 29

6-hexyloxy-1,2,3,4-tetrahydronaphthalene

A solution was prepared consisting of 7.4g (0.05 mole)of 6-hyrdoxy-1,2,3,4-tetrahydronaphthalene in 250 mL of methylethylketone. To this solution was added, 9.9g (0.06 mole) of hexylbromide, 10g (0.07 mole) of anhydrous potassium carbonate and 0.5g of potassium iodide. The reaction mixture was heated to reflux for twenty-four hours, under a nitrogen atmosphere. The reaction mixture was

allowed to cool and filtered. The volatilize were removed by evaporation.. The residue was dissolve in ethyl ether and extracted twice with 2N NaOH. The organic layer was dried with anhydrous sodium sulfate and evaporated to an oil. This yielded 6.11g of the title compound.

PMR: Consistent with the proposed structure.

MS: m/e=232

Preparation 30

4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]-4-ketobutyric acid and 4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]-4-ketobutyric acid

A solution was prepared of 6.11g (0.026 mole) of 6-hexyloxy-1,2,3,4-tetrahydronaphthalene and 3g (0.03 mole) of succinic anhydride in 250 mL of dichloromethane The solution was cooled in an ice bath and 5.3g (0.04 mole) of aluminum chloride was added in several small portions. The reaction was allowed proceed for sixteen hours at ambient temperature under a nitrogen atmosphere. The reaction mixture was poured into ice-water and the organic layer isolated. The organic was washed several times with water and dried with anhydrous sodium sulfate and evaporated to an oily solid. This yielded 6.61g of the title compounds.

PMR: Consistent with the structures and indicating a mixture of isomers. This mixture was 3:1 of the 7-substituted isomer to the 5-substituted.

MS: m/e=333 (M+1) ES+

M/e=331 (M-1) ES-

The mixture could be separated into the two isomeric components by chromatography on silica gel. However, as a matter of convenience the isomeric final products were separated, *cf.*, Examples below.

Preparation 31

4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]butyric acid and 4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]butyric acid

In a manner analogous to that described in Preparation 4, *supra*, the starting ketone was reduced to the alkyl derivative. This yielded 5.10g of the title compounds as a white amorphous solid.

PMR: Consistent with the structures indicating retention of the ratio of isomers.

MS: m/e=319 (M+1) ES+

M/e=317 (M-1) ES-

Preparation 32

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]-1-oxobutyl][iso-butyl]carbonate and [4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)]-1-oxobutyl][iso-butyl]carbonate

In a manner similar to that described in Preparation 12, *supra*, the title compounds were prepared and used without further purification in the Examples, below.

Example 31

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide and [4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide

In a manner similar to that described in Example 1, *supra*, the title compounds were prepared as a tan oil (1.2g) and a mixture of isomers which were separated in the Examples, below.

PMR: Consistent with the proposed structures

MS: m/e=361 (M) FD

Example 31A

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide

An aliquot, 600 mg, of the material from Example 31, was chromatographed on silica gel eluted with a solvent system of EtOAc and MeOH. The highest $R_f$ compound isolated was the title compound, yielding 80 mg.

PMR: Consistent with the proposed structure.

Example 31B

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide

The slower moving compound from the chromatography in Example 31A, *supra*, was isolated, approximately 80 mg.

PMR: Consistent with the proposed structure.

Example 32

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide and [4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide

In a manner similar to that described in Example 1, *supra*, the title compounds were prepared as a white amorphous solid (1.8g) and a mixture of isomers which were separated in the Examples, below.

PMR: Consistent with the proposed structures

MS: m/e=363 (M) FD

Example 32A

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide

The material from Example 32, was chromatographed on silica gel eluted with a solvent system of EtOAc-hexane (2:1, v/v). The highest $R_f$ compound isolated was the title compound, yielding 430 mg.

PMR: Consistent with the proposed structure.

Example 32B

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide

The slower moving compound from the chromatography in Example 32 was isolated and identified as the title compound, yielding 220mg.

PMR: Consistent with the proposed structure.

Preparation 33

4-[6-(1,2,3,4-tetrahydronaphthyl)]-4-keto-2,2-dimethylbutyric acid and 4-[6-(1,2,3,4-tetrahydronaphthyl)]-4-keto-3,3-dimethylbutyric acid

1,2,3,4-Tetrahydronaphthtalene was acylated with 2,2-dimethylsuccinic anhydride in a manner analogous to that described in Preparation 1, *supra*. This yielded a mixture of the title compound with 3,3-dimethylbutyric isomer. It was convenient to separate the isomers at the next step, *cf.* Preparation 34.

PMR: Consistent with the proposed mixture of isomers.

MS: m/e=261 (M+1) ES+

M/e=259 (M-1) ES-

Preparation 34

4-[6-(1,2,3,4-tetrahydronaphthyl)]-2,2-dimethylbutyric acid

In a manner similar to that described in Preparation 4, *supra*, the mixture of isomers (8.73g (35 mmol)) in Preparation 33 were reduced to the alkyl derivatives. Crystallization of the product from ether-hexane afforded the 2,2-dimethyl isomer. This yielded 4.26g (2 crops) of the title compound.

PMR: Consistent with the proposed 2,2-dimethylbutyric acid structure.

MS: m/e=264 (M+18) ES+

M/e=245 (M-1) ES-

Preparation D

4-[6-(1,2,3,4-tetrahydronaphthyl)]-2,2-dimethylbutyric acid chloride

1.5 g (6.1 mmol) 4-[6-(1,2,3,4-tetrahydronaphthyl)]-2,2-dimethylbutyric acid was dissolved in 50 mL of anhydrous

THF and 15 mL of thionyl chloride was added. The reaction mixture was stirred at ambient temperature under an anhydrous atmosphere. After sixteen hours, the volatiles were removed by evaporation and the resulting oil was used without further purification.

Example 33

[4-[6-(1,2,3,4-tetrahydronaphthyl)]-2,2-dimethylbutyryl][N-4-hydroxyphenyl]amide

All of the material from Preparation D, *supra*, was dissolved in 50 mL of anhydrous THF and 2g of 4-aminophenol was added. The reaction mixture was stirred at ambient temperature under an anhydrous atmosphere for eleven days. The reaction was evaporated to a solid and re-dissolved in EtOAc. The organic solution was washed twice with 1N HCl and then with water. The solution was dried with sodium sulfate and evaporated to a solid. The product was further purified by chromatography on silica gel eluted with a solvent mixture of EtOAc-hexane (1:1)(v/v). The title compound was isolate as 150 mg of tan solid.

PMR: Consistent with the proposed structure.

MS: m/e=338 (M+1) ES+

336 (M-1) ES-

Preparation E

4-(6-1,2,3,4-tetrahydronaphthyl)-4-oxo-2-methylbutric acid

and

4-(6-1,2,3,4-tetrahydronaphthyl)-4-oxo-3-methylbutric acid

7.6 g (50 mmol) of 1,2,3,4-tetrahydronaphthalene was dissolved in 200 mL of dichloromethane and 5.8g (50 mmol) of 2-methylsuccinic anhydride was added. The reaction mixture was cooled in an ice bath and 8g (60 mmol) of aluminum chloride was slowly added. The reaction mixture was stirred under a nitrogen atmosphere and allowed to warm to ambient temperature. After sixteen hours, the reaction was quenched with water and organic layer was removed and washed twice

with brine. The organic layer was dried with anhydrous sodium sulfate and evaporated to dryness. This yielded 6.08g of the mixture title isomers.

NMR: Consistent with the mixture of isomers.

MS: m/e=247 (M+1) ES+

245 (M-1) ES-.

Preparation F

4-(6-1,2,3,4-tetrahydronaphthyl)-2-methylbutric acid

and

4-(6-1,2,3,4-tetrahydronaphthyl)-3-methylbutric acid

In a manner similar to that used in Preparation 4, *supra*, the isomeric keto-acids were reduced to the methylene bearing acids. The crude product was chromatographed on silica gel eluted with EtOAc-hexane (1:2)(v/v). This yielded 890 mg of the title compound as a tan oil and mixture of regio-isomers.

PMR: Consistent with the proposed structure.

Preparation G

4-(6-1,2,3,4-tetrahydronaphthyl)-2-methylbutric acid chloride

and

4-(6-1,2,3,4-tetrahydronaphthyl)-3-methylbutric acid chloride

The mixture of acids from Preparation F, *supra*, was dissolved in 25 mL of anhydrous THF and 5 mL of thionyl chloride was added. The reaction mixture was stirred at ambient temperature under an anhydrous atmosphere for several hours. The reaction mixture was evaporated to a tan gum and used without further purification.

Preparation H

[4-(6-1,2,3,4-tetrahydronaphthyl)-2-methylbutyryl][N-4-hydroxyphenyl]amide

and

[4-(6-1,2,3,4-tetrahydronaphthyl)-3-methylbutyryl] [N-4-hydroxyphenyl] amide

The mixture acid chlorides from Preparation F, *supra*, was dissolved in 25 mL of anhydrous THF and 1.1g of 4-aminophenol was added. The reaction mixture was stirred at ambient temperature under an anhydrous atmosphere. After several hours, the reaction was checked by tlc and found to be complete. The reaction mixture was diluted with 50 mL of EtOAc and washed four times with 1 N HCl, then with water. The resulting organic layer was dried with anhydrous sodium sulfate and evaporated to a tan gum.

Example 34

[4-(6-1,2,3,4-tetrahydronaphthyl)-2-methylbutyryl] [N-4-hydroxyphenyl] amide

The mixture of isomers of the crude product from Preparation F, *supra*, was chromatographed on silica gel eluted with EtOAc-hexane (1:2) (v/v). The fastest moving component was separated. This yielded 80 mg of the title compound as a tan gum.

PMR: Clearly indicating the proposed structure.

Example 35

[4-(6-1,2,3,4-tetrahydronaphthyl)-3-methylbutyryl] [N-4-hydroxyphenyl] amide

The mixture of isomers of the crude product from Preparation F, *supra*, was chromatographed on silica gel eluted with EtOAc-hexane (1:2) (v/v). The slower moving component was separated. This yielded 100 mg of the title compound as a tan gum.

PMR: Clearly indicating the proposed structure.

Example 36

6-[3-[5-[1-(2-hydroxy)ethyl] tetrazoyl] propyloxy]-1,2,3,4-tetrahydronaphthalene

300mg (1.16 mmol) of the tetrazol from Preparation C was dissolved in 100 mL of methylethylketone and 240 mg (2

mmol) of 2-bromoethanol was added. Further, 420 mg (3 mmol) of anhydrous potassium carbonate was added. The reaction was stirred and heated to reflux for sixteen hours under a nitrogen atmosphere. The reaction was allowed to cool and was filtered. The solvent was removed by evaporation *in vaccuo*. The residue was dissolved in EtOAc and washed with water. The EtOAc solution was dried with anhydrous sodium sulfate and the solvent removed by evaporation. This yielded 140 mg of the title compound as a golden oil.
MS: m/e=303 (M+1) ES+

Example 37

6-[4-[5-[1-(2-hydroxy)ethyl]tetrazoyl]butyloxy]-1,2,3,4-tetrahydronaphthalene

100 mg (0.37 mmol) of the tetrazole from Preparation A was condensed with 100mg (0.83 mmol) of 2-bromoethanol catalyzed by 200 mg (1.45 mmol) of anhydrous potassium carbonate, in a manner analogous to Example XX1, *supra*. This yielded 100 mg of the title compound as an oil.
PMR: Consistent with the proposed structure.
MS: m/e=317 (M+1) ES+.

In another embodiment, the invention provides methods for the modulation of the endocannabinoid receptors with a compound of formula I. Thus, the present invention provides methods for the treatment of the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors comprising administering to a patient in need thereof an effective amount of a compound of formula I. Particularly preferred pathologic sequelae which can be treated according to the present invention include anxiety, pain, glaucoma, depression, feeding disorders, psychosis, and muscle spasms.

The term "endocannabinoid" denotes those endogenous biochemicals found *in vivo*, which are ligands for the

receptors which are modulated by the exogenous cannabinoids, such as THC. Some examples of such compounds would be anandamide, 2-arachidonoyl glycerol, palmitoylethanolamine amide, any other fatty acid amides. Other compounds are may be found in the references cited herein.

Methods of the current invention are useful for modulating endocannabinoid receptors, the term, "modulate" means to effect a biological activity due to the interaction of a compound of formula I with a receptor which is the endogenous target for the endogenous ligand, an endocannabinoid. Such effects may be either a functional agonistic response, i.e., the positive activation of the receptor, or a functional antagonistic response, i.e., the inactivation of the receptor or blockade of the receptor towards its endogenous ligand. Such effects may be produced by interaction with endocannabinoid transportors.

As used herein, the term "patient" refers to a warm blooded animal such as a mammal which is afflicted with one or more pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors. I t is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

Patients in need of such treatment are readily diagnosed. For example, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV™) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool for some of the disorders to be treated according to the present invention, including anxiety, mood disorders, such as depression, feeding disorders, such as bulimia and anorexia nervosa, and psychosis, such as schizophrenia. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for the disorders

treated according to the present invention, and that these systems evolve with medical scientific progress.

It is also recognized that one skilled in the art may affect the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors described herein by treating a patient presently afflicted with the sequelae or by prophylactically treating a patient afflicted with the sequelae with an effective amount of the compound of formula I. Thus, the terms "treatment" and "treating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the sequel described herein, but does not necessarily indicate a total elimination of all symptoms, and is intended to include prophylactic treatment of such sequelae.

As used herein, the term "effective amount" of a compound of formula I refers to an amount which is effective in treating pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors described herein.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining an effective amount, the dose of a compound of formula I, a number of factors are considered by the attending diagnostician, including, but not limited to: the compound of formula I to be administered; the co-administration of an mGlu agonist, if used; the species of mammal; its size, age, and general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of other concomitant medication; and other relevant circumstances.

An effective amount of a compound of formula I is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts are able to be determined by one skilled in the art.

Currently, there are several receptors known which are modulated by anandamide, these include but are not limited to, CB-1 and CB-2 receptors, fatty acid aminohydrolase (FAAH), an acid aminohydrolase and an anandamide transporter receptor. [See: DiMarzo *et al*, Trends Neurosci., 21, pp.521-528 (1998) and references therein.]

The CB-1 receptor is widely distributed in the central nervous system with highest concentrations in the hippocampus, striatum, and cerebellum, moderate levels in the cerebral cortex and thalamus, and low levels in the brainstem. [See: Matsuda et al., Nature, 346, pp. 561-564 (1990); Westlake et al., Neuroscience, 63, pp. 637-652 (1994); and Glass et al., Neuroscience, 77, pp. 299-318 (1997).] The CB-1 receptor is thought to be crucial to the cannabinoid pharmacology involving the central nervous system, especially as it relates to perception [See: Felder C.C., et al., Mol. Pharmacol., 48, pp. 443-450 and references therein and Felder CC, Glass M (1998) Cannabinoid receptors and their endogenous agonists. Ann Rev Pharmacol Toxicol: 38, 179-200] Compounds which modulate the CB-1 receptor by an agonistic mechanism, i.e., activate the receptor in a manner similar to that of anandamide, have been shown to be useful, e.g., US Pat. Nos. 3,987,188 and 4,087,547. Compounds which modulate the CB-1 receptor by an antagonistic mechanism, i.e., blockading the normal physiological activation of the receptor, have been shown to be useful, e.g., US Pat. Nos. 5,596,106 and 5,747,524, and EPO 0576357A. Methods for demonstrating the ability of the compounds of formula I to modulate the CB-1 receptor are elucidated in the following sources, which are incorporated by reference herein: Rinaldi-Carmona M., et al., FEBS

Letters, 350, pp. 240-244 (1994) and Felder C., et al., JPET, 284(1), pp. 291-297 (1998).

The CB-2 receptor has been linked to the immune pharmacology associated with anandamide. Agonism and antagonism of this receptor are known in the literature and methods for determining these properties likewise known [See: Rinaldi-Carmona M., et al., JPET, 284(2), pp.644-650 (1998), which is incorporated by reference herein and references cited].

Also, effects of anandamide and other endocannabinoids is noted at other receptors: the vanilloid receptor [Ross et al., FEBS Lett., 436, pp. 449-454 (1998); Melck et al., BBRC, 262, pp. 275-284 (1999); Zygmunt et al., Nature, 400, pp. 452-457 (1999); Beltramo and Piomelli, Eur. J. Pharmacol., 364, pp. 75-78 (1999)]; receptors in the spine and NMDA [Hampson et al., JPET, 276, pp. 585-593 (1996); Boger et al., PNAS, 95, pp. 4102-4107 (1998); Thomas et al., J. Neurochem., 72, pp. 2370-2378 (1999); and receptors in the periqueductal gray, ibid. In addition, the physiological and psychological effects of the other endocannabinoids such as 2-acylglycerol and palmitoylethanolamine amide have suggested the possibility of additional, as yet unidentified, cannabinoid receptors. All of these receptors constitute potential targets and utilities for the compounds of the current invention.

Agonism, antagonism, or allosteric modulation of the anandamide transporter is also within the scope of the current invention. Methods of demonstration distinguishing between agonism, antagonism, or allosteric modulation are found in: Piomelli D., et al., PNAS, 96, pp.5802-5807 (1999), which is incorporated by reference herein and references cited.

Further, assays for demonstrating the utilities for the compounds of the current invention may be found the references cited, *supra*. For example, anandamide transporter assays may be performed using mammalian cell lines, brain synaptosomes, primary neuronal and/or glial

cultures, brain slices, or *in vivo* preparations. Such assays have been used to assess potency for inhibiting the uptake of $H^3$-anandamide in the rat basophilic cell line, RBL2H3 cells using a physiological buffer solution as described by Beltramo *et al.*, *ibid.*, which is included by reference herein.

Representative compounds of formula I were tested for binding to the endocannabinoid transporter, *cf.*, DiMarzo, *ibid.* Data, $IC_{50}$, of binding to the transporter are presented below by compound example number:

| Example A | $IC_{50}$ µg |
|---|---|
| 1 | 19 |
| 2 | 15 |
| 4 | 11 |
| 20 | 26 |
| 5 | 44 |
| 6 | 32 |
| 7 | 35 |
| 21 | 89 |
| 12 | 57 |
| 18 | 58 |
| 13 | 15 |
| 19 | 68 |
| 15 | 36 |
| 16 | 329 |
| 17 | 14 |
| AM404 | 16 |
| **Example B** | **$IC_{50}$ µg** |
| 23 | 156 |
| 24 | 116 |
| 25 | 68 |
| 26 | 26 |
| 27 | 33 |
| 28 | 41 |

| | |
|---|---|
| 29 | 175 |
| 30 | 322 |
| 31B | 1 |
| 32A | 11 |
| 32B | 8 |
| 33 | 102 |
| AM404 | 28 |
| Example C | |
| 33 | 7 |
| 34 | 40 |
| 35 | 54 |
| AM404 | 25 |

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition, that is, combined with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable salts, for purposes of stability, convenience of crystallization, increased solubility, and the like.

In practice, the compounds of formula I are usually administered in the form of pharmaceutical compositions, that is, in admixture with pharmaceutically acceptable carriers or diluents, the proportion and nature of which are determined by the chemical properties of the selected compound of formula I, the chosen route of administration, and standard pharmaceutical practice.

Thus, the present invention provides pharmaceutical compositions comprising a compound of the formula I and a pharmaceutically acceptable diluent.

The compounds of formula I can be administered by a variety of routes. In effecting treatment of a patient afflicted with pathologic sequelae described above, a compound of formula I can be administered in any form or mode which makes the compound bioavailable in an effective amount, including oral and parenteral routes. For example, compounds of formula I can be administered orally, by inhalation, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, occularly, topically, sublingually, buccally, and the like. Oral administration is generally preferred for treatment of pathologic sequelae described herein.

One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the pathologic sequelae, that is, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. (*Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should

contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention may be determined by a person skilled in the art.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations typically contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 90% of the weight thereof. The amount of the compound of formula I present in such compositions is such that a suitable dosage will be obtained. The solutions or

suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Preferred compositions and preparations are able to be determined by one skilled in the art.

The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment, or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bees wax, mineral oil, diluents such as water and alcohol, and emulsifiers, and stabilizers. Topical formulations may contain a concentration of the formula I or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

In order to more fully illustrate the operation of this invention, typical pharmaceutical compositions are described below. The examples are illustrative only, and are not intended to limit the scope of the invention in any way.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

| Ingredient | Quantity (mg/capsule) |
|---|---|
| Compound of formula I | 0.1-1000 |
| Starch, NF | 0 - 650 |
| Starch flowable powder | 0 - 650 |
| Silicone fluid 350 centistokes | 0 - 15 |

The formulation above may be changed in compliance with the reasonable variations provided.

Formulation 2: Tablets

A tablet formulation is prepared using the ingredients below:

| Ingredient | Quantity (mg/tablet) |
|---|---|
| Compound of formula I | 0.1-1000 |
| Cellulose, microcrystalline | 200 - 650 |
| Silicon dioxide, fumed | 10 - 650 |
| Stearate acid | 5 - 15 |

The components are blended and compressed to form tablets.

Formulation 3: Tablets

Tablets each containing 0.1 - 1000 mg of active ingredient are made up as follows:

| Ingredient | Quantity (mg/tablet) |
|---|---|
| Compound of formula I | 0.1 - 1000 |
| Starch | 45 |
| Cellulose, microcrystalline | 35 |
| Polyvinylpyrrolidone (as 10% solution in water) | 4 |
| Sodium carboxymethyl cellulose | 4.5 |
| Magnesium stearate | 0.5 |
| Talc | 1 |

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Formulation 4: Suspensions

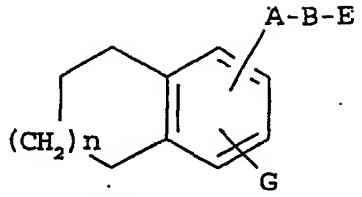
Suspensions each containing 0.1 - 1000 mg of medicament per 5 ml dose are made as follows:

| Ingredient | Quantity (mg/5 ml) |
|---|---|
| Compound of formula I | 0.1-1000 mg |
| Sodium carboxymethyl cellulose | 50 mg |
| Syrup | 1.25 mg |
| Benzoic acid solution | 0.10 mL |
| Flavor | q.v. |
| Color | q.v. |
| Purified water to | 5 mL |

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

WHAT IS CLAIMED IS:

1. A compound of the formula



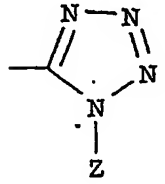

formula I

wherein

A is -O- or a direct bond;

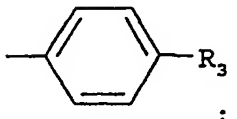
B is $C_1$-$C_8$ alkyl, $C_2$-$C_8$ alkenyl or $C_4$-$C_8$ alkenylene;

E is -COOZ, -CONR$^1$Z, or



;

Z is $C_2$-$C_8$R$^2$ or



;

R$^1$ is -H, $C_1$-$C_4$ alkyl, or $C_2$-$C_8$R$^2$;

R$^2$ each time taken, independently, is -H, -halo, -OR$^4$, -CN, or -NR$^5$R$^6$;

R$^3$ is -H, halo, or -OR$^4$;

R$^4$ each time taken, independently, is -H, -COC$_1$-C$_4$ alkyl, or -COAr$^1$ wherein Ar$^1$ is phenyl or optionally substituted phenyl;

R$^5$ is -H, -C$_1$-C$_4$ alkyl, -H, -COC$_1$-C$_4$ alkyl, or -COAr$^2$ wherein Ar$^2$ is phenyl or optionally substituted phenyl;

R$^6$ is -H, -C$_1$-C$_4$ alkyl, -COC$_1$-C$_4$ alkyl, or -COAr$^3$ wherei Ar$^3$ is phenyl or optionally substituted phenyl; or

$R^5$ taken together with $R^6$ and the nitrogen to which they are attached form a 4 to 7 membered ring;
G is -H, $-OC_1-C_8$ alkyl, $-OC_2-C_8$ alkenyl, $C_1-C_8$ alkyl, or $C_2-C_8$ alkenyl; and
n is 0-3;
and the pharmaceutically acceptable addition salts thereof.

2. A compound according to Claim 1 wherein n is 1.

3. A compound according to Claim 1 wherein E is $-CONR^1Z$.

4. A compound according to Claim 3 wherein $R^1$ is hydrogen.

5. A compound according to Claim 1 wherein Z is $C_2-C_8R^2$ alkyl, or branched alkyl.

6. A compound according to Claim 5 wherein $R^2$ is halo, hydrogen, or hydroxyl.

7. A compound according to Claim 6 wherein $R^2$ is fluoro.

8. A compound according to Claim 1 wherein Z is 4-hydroxyphenyl.

9. A compound according to Claim 8 wherein $C_2-C_8R^2$ is ethyl or propyl.

10. A compound according to Claim 1 where the A-B-E moiety is located on the 6-position of the tetrahydronaphthalene nucleus.

11. The compound according to Claim 1 wherein the compound is selected from the group consisting of
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-hydroxyethyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-3-hydroxypropyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-hydroxypropyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-2-fluoroethyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-4-hydroxyphenyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][2-hydroxyethyl]ester,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl]amide
[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-2-fluoroethyl]amide,
[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-4-hydroxyphenyl]amide,
[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-2-hydroxyethyl]amide,
[6-[6-(1,2,3,4-tetrahydronaphthyl)]hexanoyl][N-3-hydroxpropyl]amide,
[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-4-hydroxyphenyl]amide,
[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-3-hydroxypropyl]amide,
[8-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-2-fluoroethyl]amide,
[6-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]octanoyl][N-2-fluoroethyl]amide,
[6-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]hexanoyl][N-4-hydroxyphenyl]amide,

[5-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-3-hydroxypropyl]amide,

[5-[6-oxy-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-4-hydroxyphenyl]amide,

[4-[6-(1,2,3,4-tetrahydronaphthyl)]butyryl][N-4-hydroxyphenyl]amide,

[5-[6-(1,2,3,4-tetrahydronaphthyl)]pentanoyl][N-3-hydroxypropyl]amide,

[5-[4-(6-oxy-1,2,3,4-tetrahyronaphthyl)butyl]][1-N-2-hydroxyethyl]tetrazole,

[4-(5-indanyl)butyryl][N-2-hyrdoxyethyl]amide,

[4-(5-indanyl)butyryl][N-2-fluoroethyl]amide,

[4-(5-indanyl)butyryl][N-4-hydroxyphenyl]amide,

[4-(7-benzosuberanyl)butyryl][N-2-hyrdoxyethyl]amide

[4-(7-benzobuberanyl)butyryl][N-2-fluoroethyl]amide,

[4-(7-benzosuberanyl)butyryl][N-4-hydroxyphenyl]amide,

[4-(6-hexyl-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide,

[4-(6-hexyl-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide,

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide,

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide,

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide,

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-hydroxyethyl]amide,

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide,

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide,

[4-[7-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl][N-2-fluoroethyl]amide,

[4-[5-(6-hexyloxy-1,2,3,4-tetrahydronaphthyl)butyryl] [N-2-fluoroethyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]-2,2-dimethylbutyryl] [N-4-hydroxyphenyl]amide,
[4-[6-(1,2,3,4-tetrahydronaphthyl)]-2-methylbutyryl] [4-hydroxyphenyl]amide, and
[4-[6-(1,2,3,4-tetrahydronaphthyl)]-3-methylbutyryl] [4-hyroxyphenyl]amide.

12. A method of modulating an endocannabinoid receptor comprising the administration of an effective amount of a compound of Claim 1.

13. A method of modulating an endocannbinoid receptor according to Claim 12, wherein said receptor has anandamide as its endogenous ligand.

14. A method according to Claim 13, wherein said anandamide receptor is CB-1, CB-2, or the anandamide transporter.

15. A method according to Claim 13, wherein the modulation is antagonistic, agonistic, or exerts an allosteric effect.

16. A method for the treatment of the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors comprising administering to a patient in need thereof an effective amount of a compound of Claim 1.

17. A method according to Claim 16 wherein the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors is selected from the group consisting of anxiety, pain, glaucoma, depression, feeding disorders, psychosis, and muscle spasms.

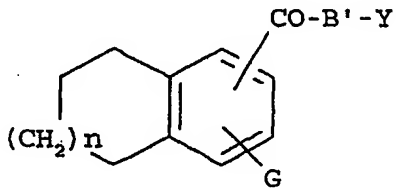
18. A pharmaceutical compositions comprising a compound of Claim 1 and a pharmaceutically acceptable diluent.

19. The use of a compound of Claim 1 as a medicament.

20. The use of a compound of Claim 1 in the manufacture of a pharmaceutical composition for the treatment of the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors.

21. A use according to Claim 20 wherein the pathologic sequelae resulting from the inappropriate regulation or modulation of an endocannabinoid receptors is selected from the group consisting of anxiety, pain, glaucoma, depression, feeding disorders, psychosis, and muscle spasms.

22. A compound of the formula




wherein

G is -H, -O$C_1$-$C_8$ alkyl, -O$C_3$-$C_8$ alkenyl, $C_1$-$C_8$ alkyl, or $C_3$-$C_8$ alkenyl;

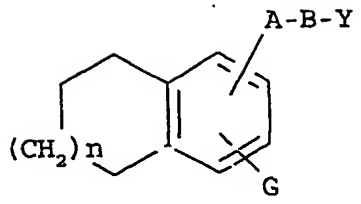
n is 0-3;

B' is a $C_0$-$C_7$ alkylene or $C_2$-$C_7$ alkenylene; and

Y is halo, -OPg, -CN, -COOPg', or -NHPg"

wherein Pg is hydroxy protecting group, Pg' is carboxyl protecting group; and Pg" is an amino protecting group.

23. A compound of the formula




wherein

A is -O- or a direct bond;

B is $C_1$-$C_8$ alkylene or $C_1$-$C_8$ alkylene;

G is -H, -O$C_1$-$C_8$ alkyl, -O$C_3$-$C_8$ alkenyl, $C_1$-$C_8$ alkyl, or $C_3$-$C_8$ alkenyl;

n is 0-3;

Y is halo, -OPg, -CN, -COOPg', or -NHPg"

wherein Pg is hydroxy protecting group, Pg' is carboxyl protecting group; and Pg" is an amino protecting group.

# INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 01/26016

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C233/22 C07C233/13 C07C233/15 C07C233/11 C07C233/29
C07C69/616 C07C57/74 A61K31/19 A61K31/165 A61P43/00
C07C235/74 C07C255/13 C07C255/29 C07C69/96 C07D257/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | SEYMOUR L. SHAPIRO ET AL.: "Indanols V. Indanoxyacetic Acid Derivatives" JOURNAL OF PHARMACEUTICAL SCIENCES., vol. 51, no. 6, June 1962 (1962-06), pages 582-584, XP002185719 AMERICAN PHARMACEUTICAL ASSOCIATION. WASHINGTON., US ISSN: 0022-3549 page 582, column 1, line 1 -column 2, line 21; table I | 1,3-6,9, 10,18, 19,23 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 December 2001 | 23/01/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016 | Zervas, B |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| X | ROBERT S. LONG: "Chromium Complexes of Azo Dyes Derived from Acylacetonitriles" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 69, no. 5, 17 May 1947 (1947-05-17), pages 990-995, XP002185722 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 993, table I, 5th compound from the bottom of the table | 22 |

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# INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/US 01/26016

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
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| X | ELAINE ISABELLE ET AL.: "Tricyclic Aromatic Ketones by Cycliacylation of Carboxylic Acid Derivatives of Indan, Tetralin, And Benzosuberane" CANADIAN JOURNAL OF CHEMISTRY., vol. 58, no. 13, 1 July 1980 (1980-07-01), pages 1344-1349, XP002185723 NATIONAL RESEARCH COUNCIL. OTTAWA., CA ISSN: 0008-4042 page 1347, column 1, line 36 - line 50 | 23 |
| X | US 2 510 740 A (LE ROY W. CLEMENCE ET AL.) 6 June 1950 (1950-06-06) example X | 23 |
| A | PIOMELLI D ET AL: "The endocannabinoid system as a target for therapeutic drugs" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 21, no. 6, 1 June 2000 (2000-06-01), pages 218-224, XP004213308 ISSN: 0165-6147 the whole document | 1,12-21 |
| A | DE 198 37 638 A (BAYER) 24 February 2000 (2000-02-24) page 18, line 20 - line 52; claims; examples | 1,12-21 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10,22,23 (all in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. Consequently, the search has been restricted to the compounds claimed in claim 11 and the compounds prepared in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

'ormation on patent family members

Inte ·nal Application No
PCT/US 01/26016

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
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| | | | WO | 0010967 A1 | 02-03-2000 |
| | | | EP | 1105370 A1 | 13-06-2001 |